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(54) (Title of the Invention) Preparation Containing Stabilized Antiulcer Agent

(57) (Abstract)

(Constitution) A preparation containing stabilized antiulcer agent, wherein amino acid, amino acid acid salt or amino acid alkali salt and buffer are blended as stabilization agents with benzimidazole compounds having antiulcer action that are unstable in acid.

(Effect) It was discovered that the benzimidazole compound is extremely well stabilized, and coloration does not occur, when amino acid, amino acid acid salt or amino acid alkali salt and buffer are used in conjunction and blended as stabilization agents in benzimidazoles that are unstable in acid. As a result, preparations containing stabilized antiulcer agent are obtained by employing these stabilization agents.

(Scope of Patent Claims)

(Claim 1) A preparation containing stabilized antiulcer agent, where amino acid, amino acid acid salt or amino acid alkali salt and buffer are blended as stabilization agents with benzimidazole compounds having antiulcer action that are unstable in acid.

(Claim 2) The preparation according to Claim 1, wherein the benzimidazole compound is 2-((2-pyridyl)methylsulfinyl)benzimidazole compound.

(Claim 3) The preparation according to Claim 1, wherein the benzimidazole compound is omeprazole, lansoprazole or 2-((4-(3-methoxypropoxy)-3-methyl-2-pyridyl)methylsulfinyl)-1H-benzimidazole sodium salt.

(Claim 4) The preparation according to Claim 1, wherein the amino acid, amino acid acid salt or amino acid alkali salt is glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-aspartic acid, L-aspartic acid sodium salt, L-lysine or L-lysine-L-glutamate, and the buffering agent is phosphoric acid alkali metal salt, sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate or aluminum glycinate.

(Claim 5) The preparation according to Claim 1, which is a tablet, granule or capsule.

(Claim 6) The preparation according to Claim 1, wherein the amino acid, amino acid acid salt or amino acid alkali salt is glycine hydrochloride, L-alanine, DL-alanine or L-glutamic acid sodium salt, and the buffering agent is sodium dihydrogen phosphate.

(Claim 7) The preparation according to Claim 1, wherein 1-2 undercoating layers are applied to a core tablet produced by blending benzimidazole compound with the amino acid, amino acid acid salt or amino acid alkali salt stabilization agent and buffering agent, whereupon enteric coating agent is applied thereupon.

(Claim 8) The preparation according to Claims 1 and 7, wherein an acidity controlling substance having buffering action, and as necessary, buffering agent, are contained in the undercoating layer.

(Claim 9) The preparation according to Claim 8, wherein the acid controlling substance having an undercoating layer buffering action is magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate or

aluminum hydroxide-sodium bicarbonate coprecipitate, and the buffering agent is sodium tartrate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, dipotassium hydrogen phosphate, sodium pyrophosphate, disodium hydrogen phosphate, trisodium phosphate or tripotassium phosphate.

(Claim 10) The preparation according to Claim 1 or 7, wherein the enteric coating agent is cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, carboxymethylethylcellulose or methacrylic acid-acrylic acid coprecipitate.

(Detailed Description of the Invention)

(0001)

(Field of Industrial Utilization) The present invention relates to a preparation containing stabilized antiulcer agent.

(Prior Art and Problems to be Solved by the Invention) Benzimidazole compounds having H^+-K^+ ATPase inhibitory action are useful as treatment agents for digestive ulcers that strongly inhibit the secretion of stomach acid. This action is strong and persistent, and these agents are thus being focused on as next-generation digestive antiulcer treatment agents that differ from histamine H_2 receptor antagonists such as cimetidine. The stomach acid secretion inhibitory action is particularly strong with the benzimidazole compounds described in Japanese Unexamined Patent Application Publication S54-141783, Japanese Unexamined Patent Application Publication S61-50978 and Japanese Unexamined Patent Application Publication H1-6270, and the utility of these compounds has been confirmed from the standpoint of clinical use. However, the stability of these benzimidazole compounds is poor, and they are unstable with respect to temperature, moisture and light when in solid form. In addition, the substances rapidly decompose and become extremely discolored in aqueous solutions that are acidic or neutral. Moreover, in preparations such as tablets, fine particles, granules, capsules and powders, the substances are affected by the other components in the preparation formula, and are thus rendered unstable. As a result, the content of compound decreases over time, and discoloration occurs. Furthermore, when the compounds are coated in the form of tablets or granules in these preparations, their compatibility with enteric bases (e.g., cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, methacrylic acid-acrylic acid copolymer) is poor, and thus a decrease in content and discoloration occur. When manufacturing oral preparations of benzimidazole compounds of this type, even if it is not necessary to blend the compounds with other components or to coat them with enteric bases, it is difficult to form a preparation due to the detrimental effects acting on stability described above. Consequently, when formulating these compounds into oral dosage forms, it is necessary to sufficiently stabilize the compounds. In the past, a large body of research has been

produced in regard to stabilization agents and stabilization methods, with the objective of obtaining a stable preparation of benzimidazole compounds having antiulcer action. Examples include methods involving the blending of alkali reactive compounds (Japanese Unexamined Patent Application Publication S62-258320), methods involving the blending of basic magnesium or calcium inorganic salts (Japanese Unexamined Patent Application Publication S62-277322) and methods involving the blending of magnesium oxide and mannitol (Japanese Unexamined Patent Application Publication H2-22225). However, the development of additional useful stabilized preparations is desired.

(0002)

(Means for Solving the Problems) The inventors of the present invention et al., in light of this state of affairs, carried out painstaking investigations regarding various stabilization agents with the objective of stabilizing compositions containing benzimidazole compounds, and arrived at the present invention upon discovering that the aforementioned problems could be solved by using amino acids and buffering agents in conjunction. Specifically, the present invention relates to a preparation containing stabilized antiulcer agent, produced by blending amino acid, amino acid acid salt or amino acid alkali salt and buffer as stabilization agents with benzimidazoles having antiulcer action that are unstable in acid. In the present invention, the benzimidazole compound that has antiulcer action and is unstable in acid is a 2-((2-pyridyl)methylsulfinyl)benzimidazole compound, and specifically, denotes the compounds described in the aforementioned various unexamined patent application publications, e.g., omeprazole (5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridyl)methyl)sulfinyl)-1H-benzimidazole), lansoprazole (2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl)methyl)sulfinyl)-1H-benzimidazole or 2-((4-((3-methoxypropoxy)-3-methyl-2-pyridyl)methylsulfinyl)-1H-benzimidazole sodium salt.

(0003) In the present invention, examples of the amino acid, amino acid acid salt or amino acid alkali salt include glycine, glycine hydrochloride, L-alanine, DL-alanine, L-threonine, DL-threonine, L-isoleucine, L-valine, L-phenylalanine, L-glutamic acid, L-glutamic acid hydrochloride, L-glutamic acid sodium salt, L-aspartic acid, L-aspartic acid sodium salt, L-lysine or L-lysine-L-glutamate. These substances may be used in conjunction, but it is preferable to use glycine, glycine hydrochloride L-alanine, DL-alanine or L-glutamic acid sodium salt. The buffer refers to an additive used for adjusting the pH to an alkaline value of pH 8-9, and examples include phosphoric acid alkali metal salts (disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, sodium dihydrogen phosphate and potassium dihydrogen phosphate), sodium tartrate, sodium acetate, sodium carbonate, sodium bicarbonate, sodium polyphosphate, sodium pyrophosphate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium carbonate, aluminum hydroxide-sodium bicarbonate coprecipitate (product name: Cumulite, manufactured by Kyowa Chemical Industries) or aluminum glycinate (product name: Glycinal, manufactured by Kyowa Chemical Industries). These substances may be used individually or in conjunction, but it is preferable to use disodium hydrogen phosphate.

In addition, the blend amounts of these substances are preferably in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffering agent per 1 part by weight of benzimidazole compound, but amounts are not restricted to these ranges. The stabilization agent of the present invention can be added in conjunction with additives that are generally used in preparations, e.g., mannitol, corn starch, crystalline cellulose and other excipients, hydroxypropylcellulose and other binders, low-substitution hydroxypropylcellulose, carboxymethyl starch sodium (product name: Explotab, Kimura Sangyo), carboxymethylcellulose calcium and other disintegration agents, sodium lauryl sulfate, Tween 80 (product name) and other surfactants, and magnesium stearate, talc and other glazes.

(0004) The composition of the present invention is obtained by uniformly blending benzimidazole compound with the amino acid, amino acid acid salt or amino acid alkali salt stabilizer and buffering agent, and as necessary, the aforementioned additives and water. However, the blending method, for example, can be carried out by blending the additives with a blend produced by blending the amino acid, amino acid acid salt or amino acid alkali salt and buffering agent beforehand with the benzimidazole compound. Alternatively, stabilizer can be added to a material produced by blending benzimidazole compound and additive, followed by bringing the stabilizer into uniform contact with the benzimidazole compound. The resulting mixture is then formed into fine particles by means of a wet-format granulation method, followed by tabletization in order to obtain base tablets for producing tablets. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules using a marmelizer (manufactured by Fuji Powder).

(0005) The core tablets or core granules obtained in this manner are then coated with an enteric coating agent to produce an enteric preparation, but in order to eliminate the detrimental effects of the enteric coating base, 1-2 layers of undercoating layers are applied onto the core tablets or core granules. Examples of undercoating bases that can be cited include hydroxypropylmethylcellulose, hydroxypropylcellulose and polyvinylpyrrolidone, and acid controllers having buffering action can be added to the undercoating layer, e.g., magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium silicate, synthetic hydrotalcite, aluminum hydroxide, aluminum glycinate and aluminum hydroxide-sodium bicarbonate coprecipitate. The aforementioned buffering agents can also be added as necessary. Examples of enteric coating agents include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, carboxymethylethylcellulose, methacrylic acid-acrylic acid copolymers (product name: Eudragit), and other such substances. In this manner, enteric tablets and granules having dosage forms appropriate for oral administration may be obtained. In addition, the granules may be loaded into capsules to produce a capsule preparation. The preparations obtained in this manner experience little change in external appearance when stored for long periods of time, and exhibit superior stability with very little decrease in active content. The preparations of the present invention have excellent stomach

acid controlling action and antiulcer action, and in addition, also have low toxicity, and thus can be used in the treatment of digestive ulcers and other ailments in mammals, including humans.

(0006)

(Examples of Embodiment) The present invention is described in additional detail below by providing experimental examples and examples of embodiment, but the present invention is not restricted by these examples.

Example of Embodiment 1

100 mg omeprazole, 100 mg of various types of amino acid and 100 mg of sodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) used as buffering agent were dispersed in 20 mL of water, and stored at 25°C. The change in external appearance over time of the white suspension was observed. In addition, the change in external appearance over time at 25°C was also investigated for a control liquid that did not contain either amino acid or buffering agent.

(0007)

(Table 1)

Table 1

		Additive (mg)		External appearance, 25°C		
				1 day	3 days	7 days
Present invention		Glycine	100	White	White	White
		$Na_2HPO_4 \cdot 12H_2O$	100			
		L-alanine	100	White	White	Gray/White
		$Na_2HPO_4 \cdot 12H_2O$	100			
		L-threonine	100	White	White	Gray/White
		$Na_2HPO_4 \cdot 12H_2O$	100			
		L-isoleucine	100	White	White	White
		$Na_2HPO_4 \cdot 12H_2O$	100			
		L-phenylalanine	100	White	White	Gray/White
		$Na_2HPO_4 \cdot 12H_2O$	100			
Control		None	--	Light purple	Purple	Dark purple
	Amino acid	Glycine	100	Purple	Purple	Dark purple
		L-alanine	100	Light purple	Purple	Dark purple
		L-isoleucine	100	Faint brown	Purple	Dark purple
	Buffering agent	$Na_2HPO_4 \cdot 12H_2O$	200	Light brown	Light brown	Light brown
		Sodium polyphosphate	200	Faint brown	Faint brown	Light brown
		Sodium pyrophosphate	200	Faint brown	Faint brown	Light brown
		Sodium tartrate	200	Light purple	Purple	Purple
		Sodium acetate	200	Faint brown	Light purple	Light purple
		Sodium hydrogen carbonate	200	White	Faint brown	Light purple
		Disodium hydrogen phosphate	200	Light brown	Light brown	Light brown
		Magnesium carbonate	200	White	Faint brown	Light brown

(0008) The results demonstrate that in comparison to amino acid or buffering agent alone, the use of the two in combination suppresses omeprazole discoloration, thus demonstrating that omeprazole is stabilized by using the two substances in conjunction.

(0009)

Example of Embodiment 1

The omeprazole, crystalline cellulose, low-substitution hydroxypropylcellulose, hydroxypropylcellulose and mannitol in the composition below were collected into a kneader, and were blended for about 20 min. An appropriate amount of purified water containing dissolved glycine and disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) was added, and kneading was carried out. Subsequently, drying was carried out at 50°C for 30 min in a fluidized dryer. After drying, the granules of 14-24 mesh were obtained using screens.

Omeprazole	5.0 mg
Glycine	2.5 mg
$Na_2HPO_4 \cdot 12H_2O$	2.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	56.5 mg
Total	75.0 mg

(0010) Example of Embodiment 2

Granules were obtained from the following composition as in Example of Embodiment 1. The L-glutamic acid sodium salt and sodium pyrophosphate were blended after dissolving in distilled water.

Omeprazole	5.0 mg
L-Glutamic acid sodium salt	2.5 mg
Sodium polyphosphate	1.0 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.0 mg
Total	75.0 mg

(0011) Example of Embodiment 3

Granules were obtained from the following composition as in Example of Embodiment 1. The L-alanine and dipotassium hydrogen phosphate (K_2HPO_4) were blended after dissolving in distilled water.

Omeprazole	5.0 mg
L-Alanine	1.5 mg
K_2HPO_4	1.5 mg
Crystalline cellulose	4.0 mg
Low-substitution hydroxypropylcellulose	4.0 mg
Hydroxypropylcellulose	0.5 mg
Mannitol	58.5 mg

Total	75.0 mg

(0012) Example of Embodiment 4

Coatings having the following compositions were applied to the granules obtained in Example of Embodiment 3 to obtain enteric granules. The undercoatings 1 and 2 were applied using a fluidized spray drying device (Okawara) at a supply gas temperature of 75°C and an exhaust gas temperature of 55°C. The enteric coating was applied at a supply gas temperature of 65°C and an exhaust gas temperature of 50°C.

Granules of Example of Embodiment 3	75.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	3.5 mg
Synthetic hydrotalcite	1.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	5.5 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.5 mg
Titanium oxide	2.5 mg
Talc	0.5 mg
Purified water	(64.5 mg)
Total	6.5 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	10.7 mg
Cetanol	0.5 mg
Talc	1.8 mg
Methylene chloride	(33.0 mg)
Ethanol	(86.0 mg)
Purified water	(33.0 mg)
Total	13.0 mg
Overall total	100.0 mg

(0013) Example of Embodiment 5

The omeprazole, mannitol, Explotab, sodium laurylsulfate and hydroxypropylcellulose in the following composition were mixed until uniform, the L-isoleucine and sodium pyrophosphate dissolved in an appropriate amount of purified water were added, and kneading was performed. The

material was dried in a fluidized dryer for 30 min at 50°C. The dried granules were sized with a 24 mesh screen, and after adding and mixing the magnesium stearate, 135 mg tablets (core tablets) were manufactured with a rotary pelletizer.

Omeprazole	20.0 mg
L-isoleucine	3.0 mg
Sodium pyrophosphate	3.0 mg
Mannitol	99.2 mg
Explotab (generic name: carboxymethylstarch sodium)	8.0 mg
Sodium laurylsulfate	0.3 mg
Hydroxypropylcellulose	1.0 mg
Magnesium stearate	0.5 mg
Total	135.0 mg

(0014) Example of Embodiment 6

Coatings having the following composition were applied to tablets (core tablets) obtained in Example of Embodiment 5, thus forming enteric tablets. The undercoatings 1 and 2 were produced using a High Coater (Freund Ind.), where coating was carried out at a pan rotation rate of 13 rpm, a supply gas temperature of 70°C and an exhaust gas temperature of 40°C. The enteric coating was applied at a supply gas temperature of 55°C, and an exhaust gas temperature of 37°C.

Tablets of Example of Embodiment 5	135.0 mg
Undercoating 1	
Hydroxypropylmethylcellulose	1.5 mg
Cumulite (generic name: aluminum hydroxide-sodium bicarbonate coprecipitate)	0.4 mg
Purified water	(23.0 mg)
Total	1.9 mg
Undercoating 2	
Hydroxypropylmethylcellulose	3.1 mg
Titanium oxide	1.0 mg
Purified water	(56.0 mg)
Total	4.1 mg
Enteric coating	
Hydroxypropylmethylcellulose phthalate	3.1 mg
Cetanol	0.2 mg
Talc	0.2 mg

Ethanol		(35.0 mg)
Purified water		(10.0 mg)
	Total	3.5 mg
	Overall total	144.5 mg

(0015) Example of Embodiment 7

The core granules indicated in the formula below were manufactured as in Example of Embodiment 1. The glycine and sodium pyrophosphate used as stabilizer were blended after dissolving in purified water. The Cumulite and disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) were blended in the undercoating (1) in order to prevent modification due to blending between the enteric coating and omeprazole in the core granules. Film coating was performed using a fluidized spray dryer (Okawara). The undercoating layers (1) and (2) were applied at a supply gas temperature of 75°C and an exhaust gas temperature of 55°C, whereas the enteric coating was applied at a supply gas temperature of 55°C and an exhaust gas temperature of 40°C.

Core granules		
Omeprazole		5.0 mg
Glycine		2.0 mg
Sodium pyrophosphate		2.0 mg
Crystalline cellulose		4.0 mg
Low-substitution hydroxypropylcellulose		4.0 mg
Hydroxypropylcellulose		0.5 mg
Mannitol		52.5 mg
	Total	70.0 mg
Undercoating 1		
Hydroxypropylmethylcellulose		3.2 mg
Cumulite (generic name: aluminum hydroxide·sodium bicarbonate coprecipitate)		1.2 mg
$Na_2HPO_4 \cdot 12H_2O$		0.1 mg
Talc		0.5 mg
Purified water		(60.0 mg)
	Total	5.0 mg
Undercoating 2		
Hydroxypropylmethylcellulose		3.5 mg
Titanium oxide		1.0 mg
Talc		0.5 mg

Purified water		(65.0 mg)
	Total	5.0 mg
Enteric coating		
Eudragit L-30D-55 (solid content)		15.0 mg
(generic name: methacrylic acid-acrylic acid copolymer)		
Polyethylene glycol 6000		1.3 mg
Tween 80		0.7 mg
Talc		3.0 mg
Purified water		(50.0 mg)
	Total	20.0 mg
	Overall total	100.0 mg

(0016)

Effect of the Invention

The use of buffering agent alone or the use of amino acid, amino acid acid salt or amino acid alkali salt alone provides absolutely no stabilization effect when the substance is blended with benzimidazole compounds. However, it was discovered that dramatic stabilization of benzimidazole compounds occurs when these two substances are used in conjunction, and that stabilized preparations containing antiulcer agents are obtained by using these substances in conjunction.